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Observations and experiments on the pathology of Graves's disease.

By Walter Edmunds, M.C.

[With Plates X—XIII.]

Microscopic examination of the enlarged thyroid constituting an ordinary goitre shows various changes; there are found—

1. A tissue differing from the normal thyroid only in being somewhat coarser.

2. Cysts, some containing colloid material, and some a papillomatous ingrowth.

3. Nævoid or erectile tissue (explaining the expansile pulsation felt in some goitres).

4. Myxomatous changes of the interacinous tissue: this tissue then stains of a pale colour, and thus contrasts with the colloid contents of the vesicles. Sometimes the vesicles contain in their centre normal dark-staining colloid, and external to this, next the lining cells, a layer which stains much more palely.

5. Tissue of an embryonic type, consisting mainly of secreting cells, and not containing either vesicles or colloid.

The goitre of Graves's disease does not differ greatly from others, but a remarkable hypertrophy of the blood-vessels is sometimes found, and the presence of the "embryonic" (small-celled) tissue is fairly constant (Plates X and XI).

This tissue resembles that of the parathyroid glands.

These glands are most easily recognised in rabbits, for in them they are situate quite apart from the thyroid proper; they are of a bright red colour, and lie one on each side of the trachea below and at a considerable distance from the thyroid. They consist mainly of secreting cells arranged more or less in columns; there are no vesicles and no colloid; these glands were first described by Sandström in 1880.

In rabbits it has long been noticed that excision of the thyroid gland is not followed by the same fatal result that attends the operation almost (though not quite) invariably in dogs and cats; but Gley has recently shown that in rabbits, if, as well as the thyroid, the parathyroid glands are removed, the animal, as a rule,

dies. These experiments of Gley's have been repeated by myself, and it was found (1) that if both the thyroid and the parathyroid glands are removed the animals die: out of a batch of seven rabbits on whom this operation was performed, five died within eight days, the other two surviving for months. (2) That when the thyroid gland only is excised, the parathyroid glands being left, many of the animals also die: in a batch of seven operated on, five died within forty-two days, and two survived for months; in another set of seventeen operations two were killed while in good health (at the fifty-second and the fifty-ninth day), and the remaining fifteen all died within ninety-seven days: in four of them there was noticed a condition resembling myxœdema in man; the general health failed, the hair fell out, and there was a remarkable œdema of the lower part of the face. (3) If the parathyroids are alone extirpated, the animals, as a rule, live, and do not undergo any obvious change, at least not for a long time. In a batch of seven, one died at the thirty-fifth day, a second the eighty-second day, and a third the one hundred and fifty-sixth day; the other four survived, but two of these now, after six months, are weak and emaciated.

The appearance of some of these parathyroidless rabbits gave rise to the suspicion that the operation caused exophthalmos, and a fresh series of experiments (with controls) was made to test this point; the result seemed clear, the operation did not cause exophthalmos,—indeed, after the lapse of six months the eyes in two or three of these operated rabbits looked sunken, as if they were suffering from the opposite condition of enophthalmos. It is therefore proposed to make another series of experiments to decide as to this.

The parathyroids after extirpation of the thyroids do not undergo any marked changes, but they may hypertrophy somewhat; under the microscope, too, there is no pronounced alteration of minute structure, they do not develop into normal thyroids, no vesicles and no colloid form.

In dogs, also, there are parathyroids, but in them these small glands lie half embedded in the substance of the thyroid itself; consequently, in excision of the thyroid lobes, the parathyroids have been removed as well. Gley found that if the parathyroids are separated and left, the animal will live, notwithstanding the removal of the rest of the thyroid lobes. The present writer's experiments (six in number) show that if the whole of one lobe of

the thyroid, including its parathyroid, and also the greater part (two thirds or more) of the other lobe be removed, the animal will live or die, according as the parathyroid is or is not left.

The parathyroid and also the portion of thyroid that is left in these experiments hypertrophy considerably.

The hypertrophied parathyroid consists only of new columns of secreting cells, and has not developed into thyroid proper: no vesicles nor colloid formed in the two specimens I examined.

The hypertrophied portion of thyroid proper contains a considerable growth of new tubules lined with a single layer of secreting cells; there also appears to be less colloid in the vesicles, as if it had been absorbed: in one case many vesicles were empty. Further, the cells lining the vesicles are greatly hypertrophied, as described by Hürthle; they have become much larger than natural, and generally both in normal and enlarged thyroids the larger cells seem the more active cells, and this throws some light on the "vacuoles" which are found in both normal and diseased thyroids in the periphery of the colloid in the vesicles. The so-called "vacuoles" are to be seen in alcohol-hardened specimens; and, from the fact that they are not present after osmium fixing, it has been supposed they are due to shrinking from the action of the alcohol: but they seem too regularly disposed for this, and their absence from the vicinity of flat (non-acting) cells points to their probably consisting of tiny portions of recent secretion which has not yet become mixed with the rest of the colloid (Plates XII and XIII, and figure, p. 8).

Greenfield has described in the thyroid of Graves's disease (1) a similar change of the secreting epithelium "from a cubical to a columnar form;" (2) "an absorption of the colloid, it being replaced by a more mucilaginous fluid;" (3) an enormous number of newly formed tubular spaces lined by a single layer of cubical epithelium.

Parathyroids also occur in the sheep, monkey, and in the human subject. Cresswell Baber has found them in the seal.

The parathyroid gland is, it is clear, of considerable importance—it is not quite so important as the thyroid gland, but, bulk for bulk, it probably is more so, as it is considerably the smaller. In a rabbit weighing 1800 grammes the thyroid weighed 220 mg., and the parathyroids together 19 mg., or about one twelfth of the thyroid.

Although the tissue of the parathyroid gland does not at all resemble that of the thyroid in its adult form, there can be little doubt that they are closely connected, not only on account of one

being able, to a great extent, to replace the other physiologically, but also because (1) the parathyroid resembles the embryonic form of the thyroid; (2) the two tissues are occasionally found side by side in the parathyroid of the dog; and (3) because they are closely connected anatomically; in the monkey the parathyroid is embedded in the substance of the thyroid.

Now it has been supposed that the symptoms of Graves's disease (other than the goitre) are due to the action of the internal secretion from the enlarged thyroid: there does not, however, exist any evidence that thyroid secretion can produce exophthalmos. The eating of the thyroid of sheep, or the receiving of the subcutaneous injection of the extract, has produced unpleasant symptoms in healthy persons; in the subjects of myxœdema an excessive dose has produced grave and, it is stated, even fatal symptoms; but it does not appear that the eye symptoms of Graves's disease are among these effects.

In animals, thyroid feeding produced, in my hands, no very obvious results, certainly no exophthalmos. To a healthy dog were given, in one day, the thyroids of sixteen sheep, without any apparent result; and to another dog were given sheep's thyroids, two per diem, for some days without effect. Also monkeys were treated daily with large doses of the extract subcutaneously without the production of obvious symptoms, except that in one case, about the time of stopping the treatment, suddenly an area of baldness appeared on each temple, extending downwards to the shoulder: this hair gradually grew again, but an attempt to reproduce the result in the same monkey by the re-application of the supposed cause, *i. e.* the administration of thyroid extract in large doses and then suddenly stopping it, failed.

If it be argued that the thyroid of Graves's disease is not merely an enlarged one, but is also altered in structure, and that therefore the secretion is also probably altered, it must be answered that that may well be, but that no evidence has yet been brought forward that this altered secretion can produce exophthalmos.

The apparent contrast between the symptoms of Graves's disease and myxœdema, coupled with the brilliant success which has attended the treatment of the latter, and also of cretinism[1] by thyroid taking, certainly helps the secretion theory. But there are one or two considerations that go against it.

[1] Plate XII, fig. 4.

1. The contrast between Graves's disease and myxœdema only holds good with chronic myxœdema: in the acute myxœdema as seen in dogs, and sometimes in monkeys, there are tremors, with attacks of dyspnœa resembling those of Graves's disease.

2. Two cases have been described (by Sollier) of the co-existence in the same patient at the same time of Graves's disease and myxœdema.

3. Thyroid feeding does not as a rule make cases of Graves's disease worse. Dr. Mackenzie tells me he tried the treatment in a series of cases without marked result in either direction. Auld has, however, recorded a case in which injurious result followed and appeared to have been caused by the treatment.

4. The difficulty of saving by thyroid treatment animals deprived of their thyroids tells against the secretion theory. Twenty dogs, whose thyroids were excised, were treated by thyroid feeding, or by the administration of the extract of thyroid: the details of the treatment were varied, and also of the operation; the thyroid in some cases was removed in stages. The total result was that only two out of the twenty were saved:[1] this is, however, more than could have been expected without treatment, judging from the experience both of myself and others. The survivals are stated to be less than five per cent.; moreover the dogs lived a few days longer than without the treatment they would have done, and the symptoms were much modified, for the acute attacks of dyspnœa and rapid breathing were absent, the animals dying of emaciation and asthenia.

In monkeys, eight were treated with thyroid extract administered subcutaneously in all cases but one; they all died in from twelve to one hundred and twenty-eight days, the average time of survival being forty-four days. The symptoms from which they suffered were those of myxœdema in monkeys as described by Horsley; they lost weight, became less lively, respiration became slower, hair fell out in places, œdema appeared in the face, and the pupil was somewhat dilated; tremors occurred, and sometimes convulsive attacks, with rigidity of limbs.

Stanley Kent's results in cats are in accord: of five submitted to thyroidectomy and treated he saved only one; and of four in which the thyroid, and also one or both testes, were removed, and the treatment followed, two died, one was killed while ill, and only one survived.

Another argument for the secretion theory is found in the cure

[1] The treatment was in both cases stopped after a few weeks without ill effect.

or amelioration of Graves's disease which now many times has followed the removal of the whole or part of the enlarged thyroid. The last to review these cases is Dr. Oppenheimer, of Baltimore, who finds a total of sixty-eight on record: of these, eighteen are said to have completely recovered; twenty-six were more or less improved; in nine there was no change either way; in five there was immediate death; and in four death followed the operation within twenty-four hours.

One case of improvement, amounting practically to cure, has come under my own observation. The case was seen almost from the commencement of the symptoms, and treated, but without success; it gradually became worse, the patient at last being very ill, with the usual symptoms, including the paroxysmal attacks of palpitation and rapid breathing. The only course that seemed left was to operate on the goitre, but before undertaking this step a consultation was held with Dr. Hector Mackenzie. He agreed in the advisability of the operation, and also in considering the spasmodic attacks to be due to the effects of the disease itself, and not to the mechanical pressure of the goitre on the trachea. The attacks resembled those which occur in thyroidless dogs. A considerable portion (but not all) of the goitre was removed; the patient was much benefited, and the symptoms gradually passed off, so that the patient was practically well, though the pulse, if counted, was found too fast, and a little exophthalmos might still have been detected on critical examination (at no time was it a prominent symptom).

It is argued that the improvement must be due to the diminution of the thyroid secretion, following the removal of a portion of the thyroid, and that therefore the symptoms are due to that cause; but it must be remembered that for these cures to take place it is not apparently necessary that the whole or nearly the whole of the goitre should be removed; in some cases only one lobe has been excised, the remainder atrophying in time. This, too, is only what occurs in operations on ordinary goitre. In a case in which about half of a considerable goitre (which was compressing the trachea) was removed, the remaining portion gradually atrophied, so that in about a year the thyroid could not be detected, and the patient was well. These latter cases can only be explained by the breaking of some vicious circle, and the same explanation may apply in the cases of Graves's disease. Moreover the improvement, as we have seen, does not always follow: Dr. Mackenzie informs me of a case

under his care of ten years' standing, in which a considerable portion of the goitre was excised in the hope of benefiting the exophthalmos, which was extreme: the patient was not improved, certainly not in the exophthalmos.

The fact that the eye symptoms of Graves's disease can be produced by a chemical poison (cocaine) may be held to support the view that a poison secreted by the thyroid might do the same.

The effects of cocaine in this connection were first pointed out by Koller, and have since been carefully studied by Jessop; the latter found that by dropping cocaine into the eye there was produced (1) proptosis, (2) absence of winking, (3) Graefe's sign, (4) local anæsthesia, (5) dilatation of pupil, (6) widening of the palpebral fissure, (7) paralysis of accommodation, (8) diminution of ocular tension.

In a case of complete facial paralysis cocaine still caused widening of the palpebral fissure, and he argues that the cocaine must act on the unstriped muscular fibres (which are supplied by the sympathetic). His experiments also show that stimulation of the sympathetic in the neck could further dilate a pupil already as fully dilated as atropine could make it; and that cocaine could also dilate a pupil fully dilated with atropine. In a case of Graves's disease he found that cocaine administered cautiously produced increased proptosis, further dilatation of palpebral fissure, and halting in the descent of the upper eyelid.

Jessop also found that in the rabbit, if the cervical sympathetic be divided, after a few days cocaine will not produce dilatation of pupil, nor proptosis, nor widening of the palpebral fissure.

The effects of cocaine injected subcutaneously in monkeys, both with and without division of the cervical sympathetic, have been tried by myself. The results in monkeys of division and stimulation of the cervical sympathetic are described by Sherrington in the 'Journal of Physiology,' and represented in the figure here reproduced.

Division of cervical sympathetic causes (1) recession of eyeball; (2) contraction of pupil; (3) narrowing of palpebral fissure; (4) œdema and flushing of skin round eye; (5) swelling of caruncle; (6) projection of pinna from side of head; (7) puckering of skin of muzzle; (8) flattening of certain hairs on forehead, which cannot then be elevated by the emotions which will raise the corresponding hairs on the opposite (normal) side of the head.

Stimulation of the cervical sympathetic, on the other hand, produces (1) proptosis of the eyeball; (2) dilatation (well marked) of pupil; (3) widening of palpebral fissure; (6) lying back of pinna; (8) erection of certain hairs on forehead.

The solution of cocaine used was the hydrochlorate, and it was found that two grains of the salt (= 0·13 gramme) was fatal to a monkey. Immediately after the injection he jumped about in an excited manner; then his movements became less precise, and soon

Shows effects on division of right cervical sympathetic nerve. Sketch by Lapidge, *ad nat.*

he had to hold on to the side of his cage to retain the erect attitude; then his hold relaxed, and he collapsed on the floor of the cage, and had a succession of attacks of clonic spasms, during which the arms were extended and the hands clenched, the head partly thrown back, and the upper eyelids retracted. These attacks lasted about four seconds, with intervals of fifteen seconds. Gradually the respiration became feebler, and notwithstanding artificial respiration he died in twenty minutes or half an hour from the time of injection. After death it was noticed that the eyelids were unusually widely open, the upper eyelid being retracted, and that the eyes were prominent

(as shown by comparison with a normal monkey). Half an hour after death the cornea was still clear and convex instead of hazy and flaccid, as it usually becomes.

The cocaine experiments were made on twelve monkeys altogether. The drug was injected subcutaneously in half-grain doses (= 0·032 gramme) once a day, but it being found that this when continued produced death, the dose in the later experiments was reduced to a third or a quarter of a grain. Five of the monkeys died certainly from the effects of the injections, and three others probably from the same cause; two of the five died in convulsions.

The effect of the injections caused the animals to seem dull and to lie down,—indeed, they appeared unable to stand. Sometimes there ensued an attack of convulsions; these effects passed off in about an hour, and there remained exophthalmos, dilatation of the pupil, and widening of the palpebral fissure, and (as was thought) increased intra-ocular tension.

In three cases thyroid extract was injected as well as cocaine, but its addition made no difference that could be detected. When the cocaine injections were stopped the symptoms at once ceased: it seemed impossible to start a disease in any way resembling exophthalmic goitre by administration of cocaine or thyroid extract, either separately or together.

In seven of the monkeys, a few days before commencing the cocaine injections, a long piece of the sympathetic nerve in the neck was excised. The effects of the excision were to produce contraction of the pupil (which came on as the effects of the anæsthetic passed off) and retraction of the eye; the effect of cocaine subcutaneously on such a monkey is to greatly dilate the pupil on the normal side, and to cause proptosis there. On the operated side the pupil is somewhat dilated, but not so much; apparently no proptosis is produced, but it is not easy to be absolutely certain of this, as the opposite side is no longer normal for comparison; if there is any proptosis it certainly is not much, for the eye is not nearly so prominent as on the unoperated side. This effect of division of the sympathetic is very important, for it affords an indication for treatment in these cases of Graves's disease, in which the prominence of the eye is so great as to cause ulceration of the cornea. The usual treatment is to partially or wholly close the palpebral opening by suturing the eyelids together, but this is not always successful; sometimes, notwithstanding this, and also strapping the lids toge-

ther, the cornea sloughs and the eye (or even both eyes) is lost. The effects of paralysis of the sympathetic in man are not serious—contraction of pupil and absence of perspiration on that side; the affection is generally only discovered accidentally.

The effects of cocaine, then, it must be admitted, show the possibility of a poison being secreted by the thyroid which might cause symptoms like those of Graves's disease.

The real issue is whether the goitre of Graves's disease is primary, and by its secretion the cause of the other symptoms, or whether the disease is primarily of nervous origin.

In favour of the latter view it may be said that the relations of the disease are not so much thyroidal as neurotic.

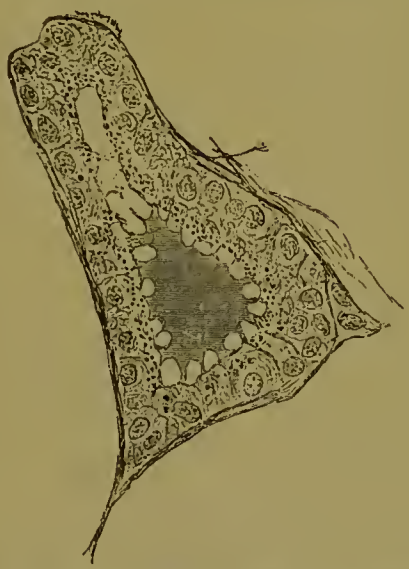
It seems to be generally agreed that it is not more common in goitrous districts than elsewhere. On the other hand, it has many nervous connections. Solbrig relates the case of a boy aged eight (the son of a woman who suffered from the disease), who, after a disappointment at school, was seized with palpitation and profuse sweating: the next day the thyroid was large, the eyes prominent, and the pulse 180. Two days later the symptoms gradually disappeared, and in ten days he was well again. Putnam cites from Coggeshall an exactly parallel case. The patient was a young girl, and the symptoms followed immediately on great excitement attending a whipping, but subsided in a few days.

Again, certain experimental lesions of the central nervous system (of the restiform bodies) have been stated by Filehne and Bienfait to be capable of causing the symptoms of Graves's disease, namely, tachycardia, exophthalmos, and hyperæmia of the thyroid (but not a definite goitre). Further, Mendel found *post mortem*, in a case of Graves's disease, atrophy of one restiform body.

The disease, too, has some relations with diabetes. Dr. Acland had recently under his care in St. Thomas's Hospital a patient suffering from diabetes, and passing between four and five ounces of sugar in the twenty-four hours. Eighteen months previously the patient had been admitted with Graves's disease, suffering from a considerably enlarged thyroid and palpitation; on his second admission the thyroid was much smaller, though still enlarged, and the palpitation absent though the pulse was still quick.

An irritation of the sympathetic nerve, either applied to its origins in the central nervous system (brain or cord) or to its prevertebral ganglia, would readily enough account for both the cardiac and the

ocular symptoms: as to the hypertrophy of the thyroid, it has been shown that stimulation of the sympathetic causes an increased secretion of the solid constituents of the saliva; the thyroid closely resembles the salivary glands, differing from them mainly in not draining through a duct, and it may be conjectured that prolonged stimulation through the sympathetic might cause the hypertrophic changes. The thyroid contains similar granules to those found in the secreting cells of the parotid gland (see figure).



Vesicle of thyroid, showing granules near inner side of secreting cells, resembling salivary glands. The vacuoles in the colloid are also shown.

Again, occasionally the eye symptoms are unilateral, and then the hypertrophy of the thyroid is generally greater on the same side as the affected eye. It was so in a case recorded by Maher, of Sydney.

The recovery in which Graves's disease in many cases terminates seems to negative any pronounced central lesion, and we need not therefore be surprised that none has been with certainty yet established.

Somewhat against the secretion theory is the fact that no poison can be found in the blood or spleen in experimental athyroidea. The blood from a dog dying of acute myxœdema, following thyroidectomy, was drawn and defibrinated, and injected into a normal dog: no effect—certainly no permanent effect—was produced. This experiment was tried five times. Also the albumoses

were extracted from the spleens of dogs dead of athyroidea. Mr. White, Pharmaceutist to St. Thomas's Hospital, kindly did this for me. The principle of the method depends on the facts that alcohol precipitates in the spleen the albumoses, the albumins, and the globuloses. At the end of about three months the last two are insoluble in water, while the albumoses are still thus soluble. They are dissolved, and the bulk is concentrated by evaporation at a low temperature and barometric pressure, and precipitated again by alcohol, and this is repeated several times in order to obtain a pure product: the albumoses thus obtained were injected into guinea-pigs with an entirely negative result.

The experiments related above were made at the Brown Institution, and the writer has much pleasure in expressing his thanks to the Institution for the opportunities afforded him. *May 21st*, 1895.

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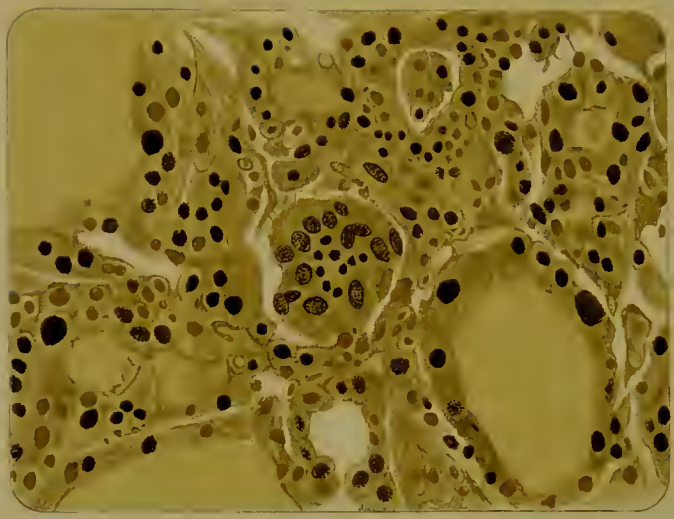

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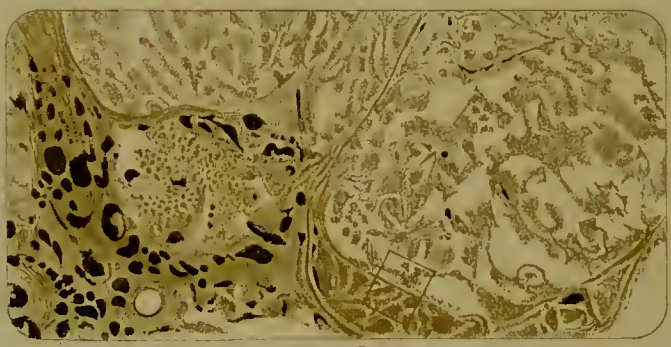


Fig. 2.

Fig. 3.

DESCRIPTION OF PLATE X,

Illustrating Mr. Walter Edmunds' Observations and Experiments on the Pathology of Graves's Disease.

Fig. 1.—Section from the goitre of Graves's disease. A portion of the hypertrophied goitre was removed by operation; it is the second case referred to in the text. The large amount of young tissue between the vesicles will be noticed; also the great hypertrophy of the nuclei of the secreting cells, and the multiplication of these cells. (× 380.)

Fig. 2.—Section of the goitre in a fatal case of Graves's disease. A drawing under a low power. On the right and also on the left above is seen capillary ingrowth into the enlarged vesicles. Below, in the centre, is a lobule, which in the absence of colloid-containing vesicles resembles accessory thyroid tissue. (× 25.)

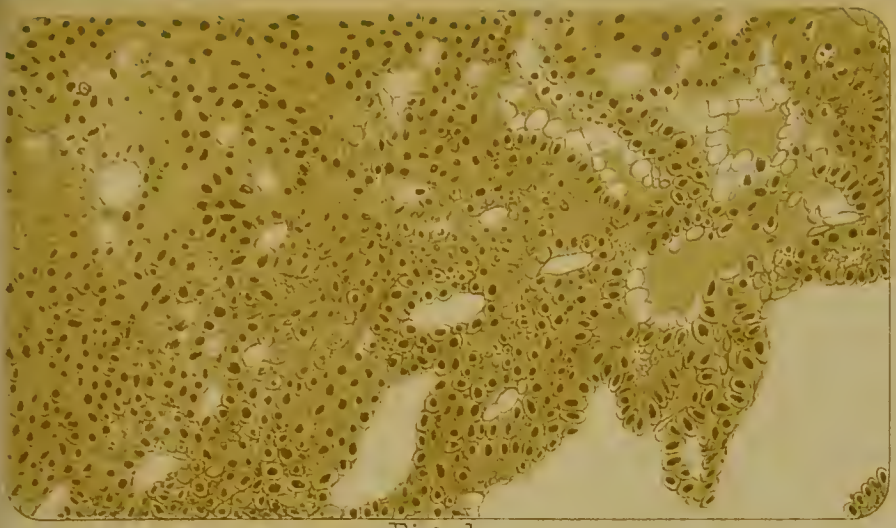
Fig. 3.—The portion of the section marked with a square in Fig. 2, more highly magnified. (× 225.)

DESCRIPTION OF PLATE XI,

Illustrating Mr. Walter Edmunds' Observations and Experiments on the Pathology of Graves's Disease.

Fig. 1.—Section of the enlarged thyroid in a case of Graves's disease. It will be seen that there is a considerable area of secreting tissue, the cells of which are arranged so as to constitute tubes, and in which there are few vesicles containing colloid. In the periphery of the colloid in the vesicles are clear spaces; the nature of these "vacuoles" is discussed in the text. Below and to the right is seen part of an enlarged vesicle; its ramifying shape shows that the fluid in it could not have been under much tension. (× 220.)

Fig. 2.—Section from an adenoma of thyroid, removed by operation. The vesicles are enlarged, and the secreting cells lining them are multiplying and penetrating into the colloid, which has completely disappeared from the upper extension of the vesicle in the centre. The connective tissue between the vesicles is coarse in structure. (× 220.)



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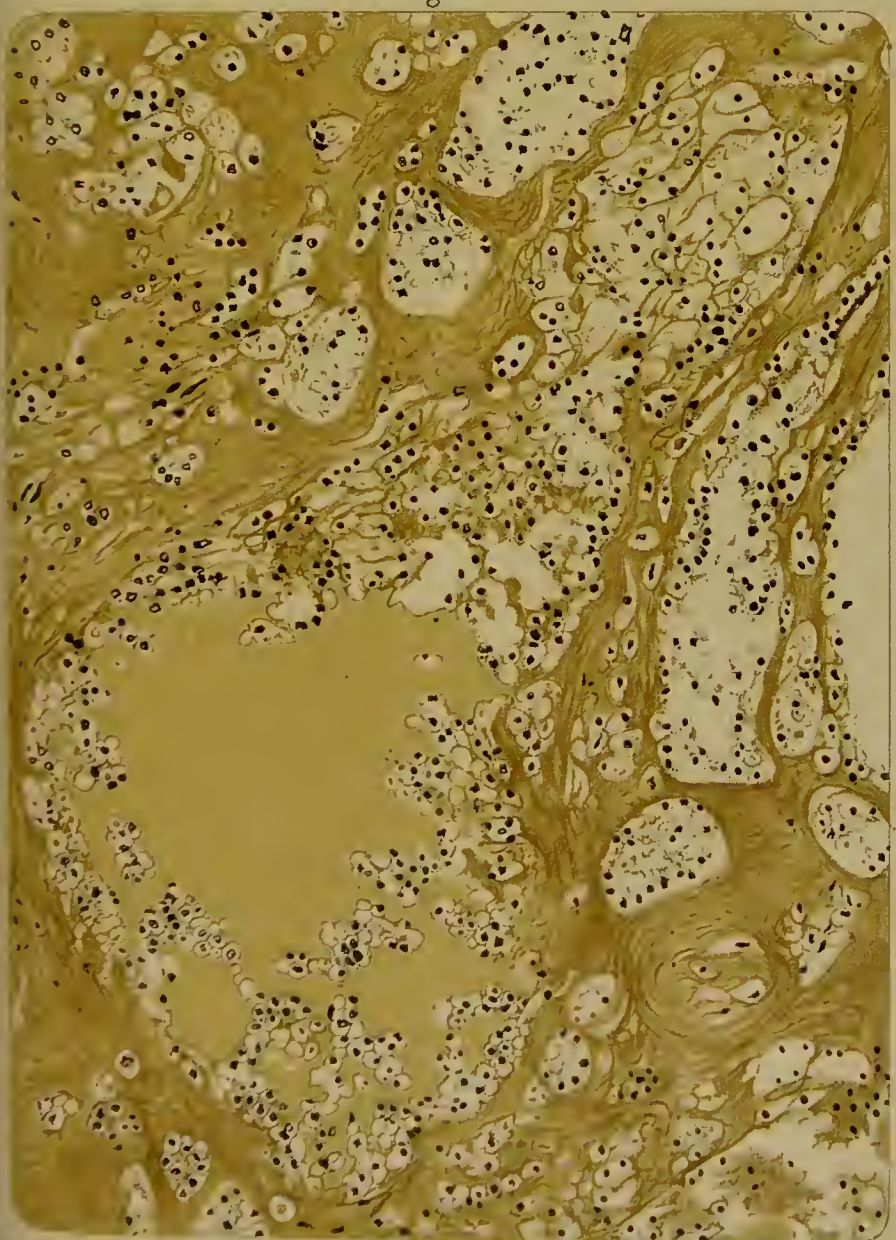

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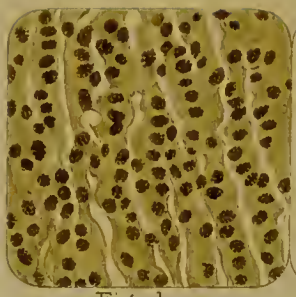

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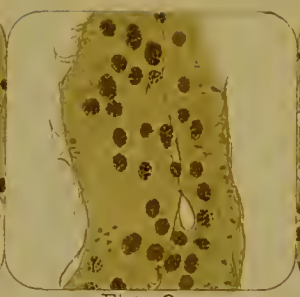

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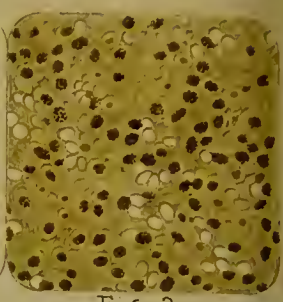

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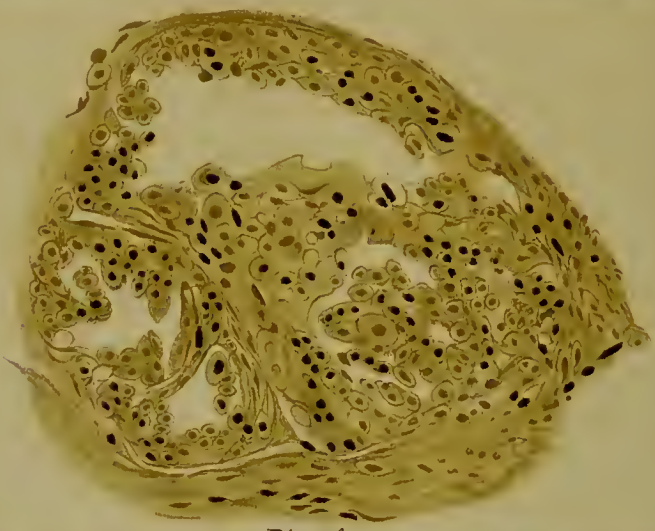

Fig. 4.

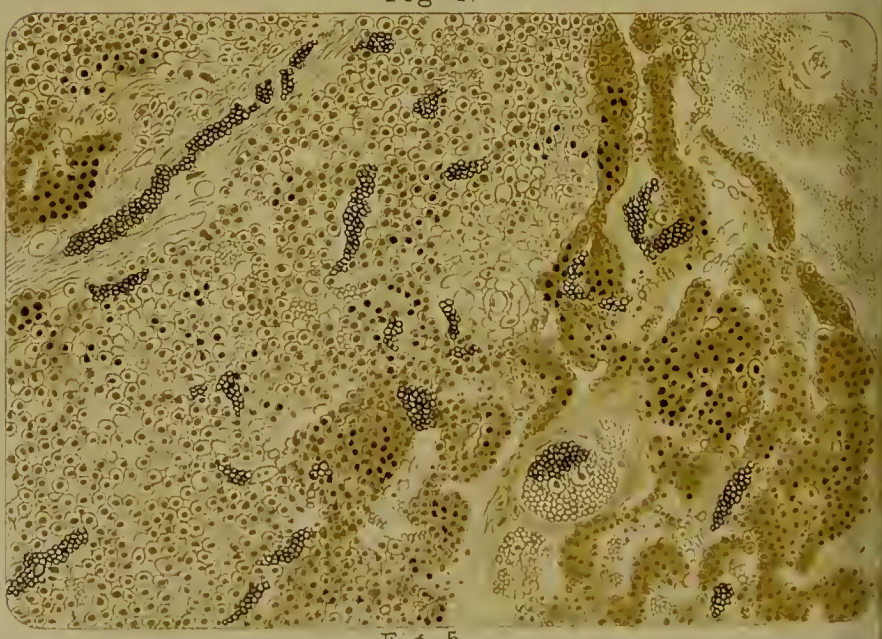

Fig. 5.

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DESCRIPTION OF PLATE XII,

Illustrating Mr. Walter Edmunds' Observations and Experiments on the Pathology of Graves's Disease.

Fig. 1.—Section of accessory thyroid of rabbit. 102 days previous to the rabbit being killed, and this specimen obtained, the whole of the thyroid proper of the rabbit had been removed, leaving only the two parathyroids. These after death were found not to be much, if at all, hypertrophied, nor was their microscopic structure materially altered; no vesicles and no colloid were seen. (× 380.)

Fig. 2.—The whole of one lobe, including the parathyroid and the greater part of the other lobe (excluding the parathyroid) of the thyroid of a dog was excised. No symptoms followed, and at the end of nine days the dog was killed. The figure represents, highly magnified, the lining (secreting) membranes of two adjacent vesicles back to back. It will be noticed that the membranes are greatly hypertrophied, and that this is effected by the enlargement of the cells rather than by their multiplication. Contrast with Fig. 4. Plate XIII, fig. 1, is from the same specimen as this figure. (× 500.)

Fig. 3.—Section of normal accessory thyroid of rabbit. It contains no vesicles and no colloid. The clear spaces are probably due to drops of secretion, but this does not stain in the same way that the colloid in the thyroid proper of the rabbit does. (× 380.)

Fig. 4.—Secretion of the thyroid of a cretin. It was obtained from the body of a girl aged ten, who was the subject of cretinism. The thyroid did not appear atrophied. The sections show little colloid in the vesicles, but there is a considerable multiplication of the secreting cells lining the vesicles. Contrast this with Fig. 2. It would seem that there is some antagonism between the multiplication of the cells and the performance of their secreting function. I am indebted to Mr. Bidwell for this specimen. (× 250.)

Fig. 5.—Section of small nodule from the surface or vicinity of the normal thyroid of man. (The patient died of phthisis.) It will be noticed that there are no vesicles and no colloid, and that the structure consists mainly of columns of cells, thus resembling the structure of the embryonic thyroid, and also of the parathyroid as seen in various mammals. (× 220.)

DESCRIPTION OF PLATE XIII,

Illustrating Mr. Walter Edmunds' Observations and Experiments on the Pathology of Graves's Disease.

FIG. 1.—From same specimen as shown in Plate XII, fig. 2. Section of small portion of thyroid left after the removal of the greater portion of the thyroid of the dog nine days previously. The thickening of the secreting linings of the vesicles and the absence of colloid from many of the vesicles is noticeable. (× 25.)

FIG. 2.—Transverse section of the normal parathyroid of the dog. It is seen half embedded in the thyroid proper, shown above and to the right. It contains no vesicles and no colloid, which latter in the thyroid proper is conspicuous by the dark colour which it has stained. (× 50.)

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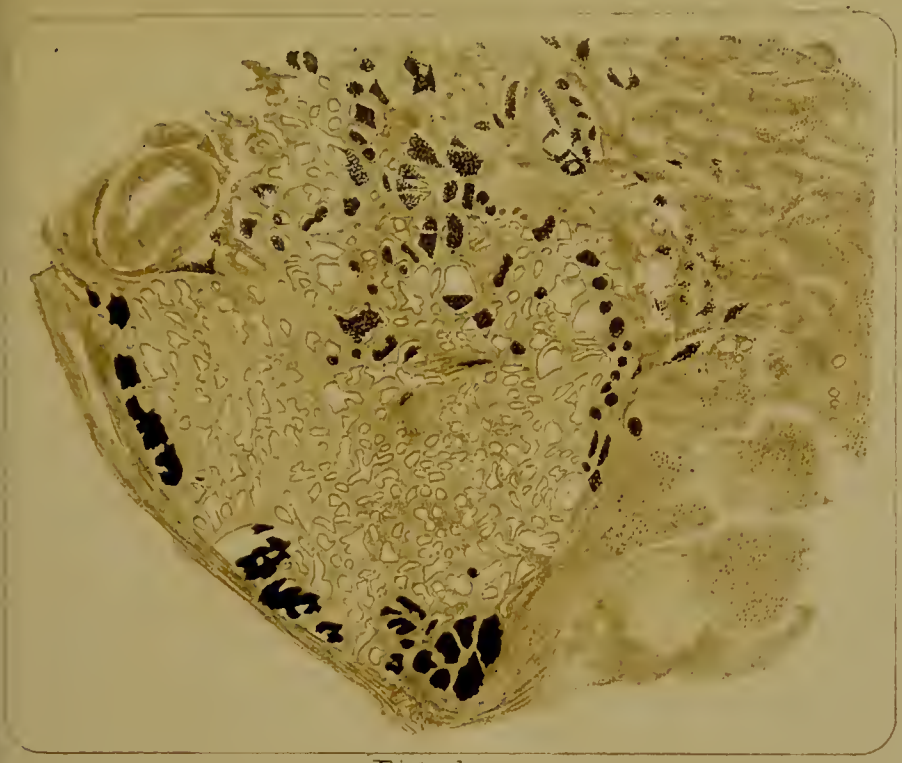

Fig. 1.

Fig. 2.

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